Feline Idiopathic Cystitis

S. Dru Forrester, DVM, MS[a,*], Todd L. Towell, DVM, MS[b]

KEYWORDS

• Lower urinary tract signs • Diagnosis • Evidence-based treatment • Stress
• Nutrition • Environmental enrichment

KEY POINTS

- Complex interactions between the bladder, neuroendocrine system, and the cat's environment seem to be involved in the pathogenesis of feline idiopathic cystitis (FIC).
- FIC is diagnosed by excluding other causes of LUT signs.
- For cats with FIC, the highest grade of evidence supports nutritional management with a multipurpose therapeutic urinary food, environmental enrichment, and feeding moist food.

INTRODUCTION—DEFINITION/TERMINOLOGY

It has been said that a well-defined problem is half solved. Perhaps feline idiopathic cystitis (FIC) remains the most common cause of feline lower urinary tract (LUT) signs, in part, because it is so difficult to define. Historically, the term feline urologic syndrome was used to describe cats with the typical clinical signs of LUT dysfunction as well as partial or complete urethral obstruction.[1] In the early 1990s, results of studies focused on identifying abnormalities of the LUT led to the suggestion that affected cats represented a naturally occurring model of interstitial cystitis (IC), a chronic LUT syndrome in people. By 1996, the term "feline interstitial cystitis" was proposed to describe cats with idiopathic LUT signs.[2] Although it remains a diagnosis of exclusion, studies over the last 2 decades suggest that FIC is a result of complex interactions between the urinary bladder, nervous system, adrenal glands, husbandry practices, and the environment in which the cat lives.[3] This syndrome is further complicated by the fact that signs can be acute or chronic and have been associated with various combinations of abnormalities in the lumen of the LUT, the LUT itself, and other organ systems that cause LUT dysfunction.[4] Comorbid conditions related to the gastrointestinal tract, respiratory system, skin, central nervous system, cardiovascular

Disclosures: S.D. Forrester is a full-time employee at Hill's Pet Nutrition, and T.L. Towell is a former employee of Hill's Pet Nutrition.
[a] Department of Global Professional & Veterinary Affairs, Hill's Pet Nutrition Inc, 400 Southwest 8th Avenue, Topeka, KS 66603, USA; [b] Global Veterinary Consulting, Erie, CO 80516, USA
* Corresponding author.
E-mail address: Dru_Forrester@hillspet.com

Vet Clin Small Anim 45 (2015) 783–806
http://dx.doi.org/10.1016/j.cvsm.2015.02.007 vetsmall.theclinics.com
0195-5616/15/$ – see front matter © 2015 Elsevier Inc. All rights reserved.

system, and the immune system are also recognized in cats with FIC.[5–9] Despite decades of research, it is still unclear if FIC is a single disease entity or a syndrome with multiple causes. The increasing evidence for multisystem involvement and evolving complexity of this diagnosis has recently led one investigator to suggest use of the term "Pandora syndrome."[4] A diagnosis of Pandora syndrome would apply to those cats that exhibit the following:

- Signs of LUT dysfunction and clinical signs in other organ systems
- Waxing and waning of clinical signs associated with stressful events
- Undergone resolution of severity of clinical signs following effective environmental enrichment

It is postulated that by broadening the name used to describe cats with chronic FIC, clinicians will be encouraged to conduct more comprehensive diagnostic and therapeutic evaluations. Ultimately, this may lead to better outcomes for affected cats and their owners.

EPIDEMIOLOGY/RISK FACTORS

A variety of identifiable causes of LUT dysfunction have been reported in cats, including urolithiasis, urethral plugs or strictures, trauma, bacterial cystitis, and neoplasia. When standard diagnostic evaluation fails to identify an underlying cause, cats are classified as having idiopathic feline LUT disease or FIC. Remarkably, in well over half of nonobstructed cats with signs of LUT dysfunction, the exact cause is unknown. In the last 25 years, 8 studies representing data from 23,837 affected cats from North America, Europe, and the Far East have identified underlying causes of LUT dysfunction.[10–17] FIC is the single most common diagnosis in these prospective (n = 627), retrospective (n = 302), and case-controlled (n = 23,019) studies (**Fig. 1**).

Although the aforementioned studies grouped together all unobstructed cats without an identified underlying cause, it is important to understand that cats ultimately diagnosed with FIC may have a variety of clinical presentations, including urethral obstruction (15%–20%) or nonobstructive disease with acute self-limiting episodes (80%–90%), frequently recurring episodes (2%–15%), or chronic persistent episodes (2%–15%).[18] Whether these presentations represent a spectrum of clinical manifestations associated with similar etiologic factors or entirely different disease mechanisms remains to be determined.

At least 5 studies have reported risk factors for development of LUT signs in general without differentiating the underlying causes.[14,16,17,19,20] Recognized breed predispositions are variable and appear to be somewhat dependent on the geography/breed popularity. One large study in the United States found that compared with domestic shorthair cats, Persian, Manx, and Himalayan cats had increased risk, and Siamese cats had decreased risk for LUT signs.[14] A similar pattern of risk was observed in Sweden for Persian (increased) and Siamese (decreased) cats.[21] Conversely, Siamese, along with Persian cats, were the most common purebred breeds affected in a New Zealand study, and the first epidemiologic study of LUT signs in Thailand reported that most cats (81.4%) were Siamese-mixed breed.[17,19] In most studies, middle-aged (4–7 years), neutered, and overweight cats are at increased risk for LUT signs.

In studies that have evaluated risk factors specifically for cats with FIC,[6,22,23] or as part of studies evaluating all causes of LUT dysfunction,[11,12,14,16] numerous risk factors have been identified (**Table 1**). Most of these studies report that male, middle-aged (~2–7 years), overweight cats are at increased risk. A variety of husbandry/environmental risk factors, most indicative of indoor housing and increased

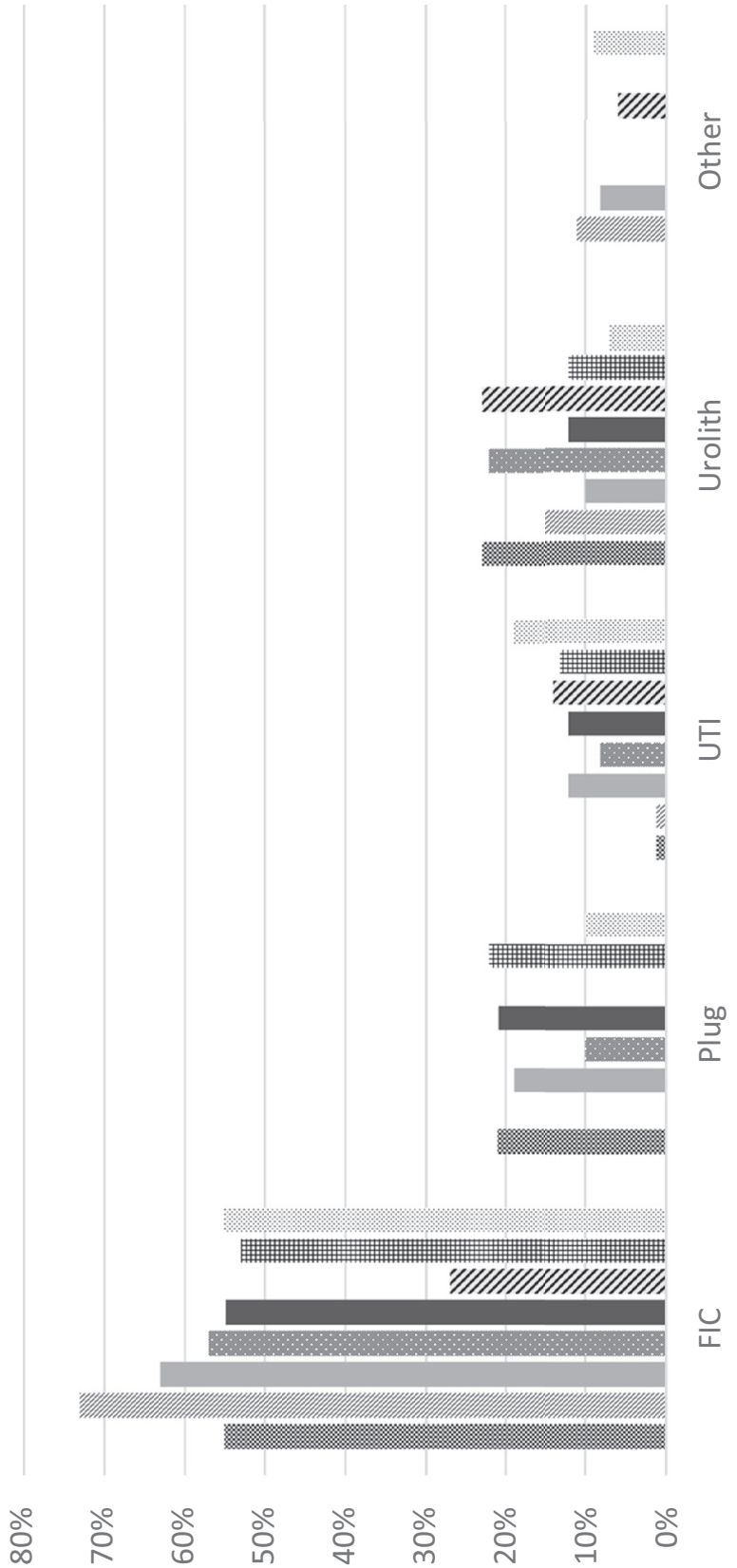

Fig. 1. Prevalence of different causes of LUT dysfunction in 8 studies from North America, Europe, and Thailand. Other, trauma, neoplasia, anatomic abnormality, urinary incontinence, chemical-induced or drug-induced inflammation, and neurogenic causes; Plug, urethral plug or obstruction; UTI, bacterial urinary tract infection. (*Data from* Refs.[10–17])

Table 1
Summary of risk factors for feline idiopathic cystitis

Risk Factor	Lekcharosensuk[14]	Cameron[22]	Gerber[12]	Buffington[6]	Saevik[16]	Defauw[23]	Dorsch[11]
Neutered	Yes	No	Yes	No	Yes	No	NA
~2–7 y	Yes	No	Yes	Yes	Yes	Yes	Yes
Breed	No	Yes	NA	No	Yes	No	No
Gender	Male	Male	Male	No	Male	Male	Male
Dry food[a]	NA	No	Yes	No	No	No	No
Overweight	NA	Yes	Yes	NA	NA	Yes	Yes
Environment[b]	NA	Yes	Yes	Yes	Yes	Yes	Yes
Comorbid disease	NA	NA	NA	Yes	NA	NA	NA
Stress[c]	NA	Yes	NA	Yes	NA	Yes	NA

Abbreviation: NA, not available.
[a] >50% of diet dry food.
[b] Factors include indoor only, litter box use, time owned, multicat household, low activity, no hunting behavior, lower water intake.
[c] Stress defined as conflict with other cats, nervous, fearful, house move.

stress, are also consistent findings. Interestingly, one investigator has demonstrated that there are deficiencies in the way most owners manage indoor cats. As a result, in the absence of specific environmental enrichment, it is likely that modern household environments are inherently stressful to most cats.[24] It is becoming increasingly evident that the interaction between cat-related factors and environmental factors is important for expression of LUT dysfunction, especially FIC.[6] Although the effect of environment/husbandry and stress in cats with LUT signs alone is not enough to cause FIC, when susceptible cats are housed in deficient environments, FIC is more likely to occur.[23]

PATHOPHYSIOLOGY

The underlying cause of FIC is unknown, and given the spectrum of presentations and manifestations, it is probable that FIC is a syndrome with multiple causes rather than a single entity. Although it is not yet possible to differentiate cause from effect or incidental finding, there is a growing body of evidence that suggests both local bladder abnormalities and neuroendocrine changes are important in the pathophysiology of FIC.

Bladder Abnormalities

Studies suggesting that human IC patients have an abnormal degree of urothelial permeability have led to similar investigations in cats with FIC.[25–28] In a healthy bladder, the mucus layer contains glycosaminoglycans (GAGs) and glycoproteins, which form a barrier preventing leakage of urine through the urothelium. One proposed pathogenic mechanism in human patients with IC involves disruption of the mucus layer, which allows the migration of urinary solutes across the epithelium. Of particular concern is potassium, which is thought to depolarize nerves and muscles and cause tissue injury.[27] Studies in cats with FIC have documented decreased concentrations of urinary GAGs.[29–31] Similar to human IC patients, the epithelial barrier of bladders from FIC cats has been shown to be compromised, allowing increased penetration of irritating protons and potassium ions from urine to the submucosa, which may stimulate sensory neurons.[32,33] Decreased urine volume and frequency of urination may further complicate FIC by allowing increased contact time of highly concentrated urine with uroepithelial tissue. Numerous cat-related and environmental factors may contribute to altered voiding frequency and increased urine concentration, including decreased water consumption (taste, availability, temperature), confinement, impaired mobility (obesity, arthritis, or illness), dirty or poorly available litter boxes, and intercat aggression. A growing number of additional local bladder abnormalities have been identified in cats with FIC (**Table 2**).[34–42] Although it is not yet understood if these changes are a cause or effect or both, these studies provide additional insight into potential pathologic processes and therapeutic targets.

Neuroendocrine Abnormalities

Recent studies suggest that stress is integrally involved in the pathogenesis of FIC. As first described by Dr Hans Selye, stress is the nonspecific response of the body to any nocuous agent or "stressor."[43] Stressors may be physical, chemical, or psychological in nature. In both humans and animals, physical and emotional stresses are involved in the pathophysiology of a variety of chronic relapsing conditions, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and IC/painful bladder syndrome.[44–47] Corticotropin-releasing factor (CRF) seems to play a central role in the behavioral and neuroendocrine responses to stress. There is convincing evidence

Table 2
Summary of reported urinary bladder abnormalities in cats with feline idiopathic cystitis

Reference	Finding	Significance
Altered tissue/urine concentration of inflammatory or bioactive molecules		
Lemberger et al,[37] 2011	Urine fibronectin content is increased in FIC cats vs control cats and those with urinary tract infection or urolithiasis	Urine fibronectin may serve as biomarker for the diagnosis of FIC
Lemberger et al,[38] 2011	Decreased Trefoil factor 2 was documented in cats with FIC vs healthy controls	Decreased Trefoil factor leads to impaired repairing abilities and may serve as a biomarker for the diagnosis of FIC
Treutlein et al,[41] 2012	Alterations were identified in expression level and pattern of numerous copurified proteins of fibronectin (C4a, galectin-7, I-FABP, thioredoxin, and p38 MAPK in urine and bladder tissue from FIC cats)	Changes indicate a role of these proteins in the pathogenesis of FIC and may provide a starting point for novel therapeutic approaches
Treutlein et al,[40] 2013	Urine total protein was transiently higher in obstructive FIC, whereas urine fibronectin and thioredoxin remained increased for 3 mo	Persistently increased fibronectin and thioredoxin may reflect ongoing structural or functional alterations in urinary bladders of cats with obstructive FIC
Neurologic abnormalities		
Buffington et al,[34] 2002	FIC bladders had significantly increased norepinephrine content and efflux in absence of alterations in acetylcholine. Adrenoceptor function was also altered in response to increased sympathetic stimulation	Other studies have identified increased sympathetic nervous system activity in cats with FIC. This study identifies the effect of increased sympathetic activity on bladder function in cats with FIC
Ikeda et al,[36] 2009	Mucosal layer of bladders in cats with FIC have increased spontaneous Ca^{2+} activity and are hypersensitive to low-dose muscarinic receptor agonists	Changes in expression or sensitivity of mucosal muscarinic receptors may contribute to FIC signs
Wu et al,[42] 2011	No evidence of overactive bladder was identified but there was significantly increased maximal urethral closure pressure and maximal urethral pressure in all portions of urethra in FIC cats	Medications for overactive bladder are not indicated for cats with FIC but α_1-adrenoceptor antagonists or skeletal muscle relaxants may be useful
Histologic changes in urinary bladder wall		
Hostutler et al,[35] 2005	Typical changes in the bladder include edema, hemorrhage, and dilation of blood vessels in the submucosa	Changes are nonspecific and not diagnostic for FIC
Sant et al,[39] 2007	Bladder mast cells are increased in FIC cats	Increased urothelial permeability with influx of potassium ions may lead to sensory afferent nerve upregulation and mast cell activation, which further stimulates afferent nerves in a vicious cycle

that an important aspect of both the onset and the exacerbation of IBS and IBD is local CRF-related peptide signaling, which results in altered permeability of the intestinal epithelial lining.[48] A similar mechanism may also be involved in the pathogenesis of FIC in cats. One theory postulates that chronic stress in susceptible cats results in an uncoupling of the normal stress response, producing an enhanced sympathetic nervous system outflow and suppressed adrenocortical responses, leading to increased sensory stimulation and altered urothelial permeability.[49] The altered hypothalamo-pituitary-adrenal (HPA) response in FIC cats is characterized by exaggerated catecholamine release and blunted cortisol response (**Fig. 2**). Support for this mechanism comes from studies that have documented the following alterations in the HPA axis and bladder in cats with FIC compared with healthy cats:

- Increased concentration of CRF in cerebrospinal fluid[50]
- Increased adrenocorticotrophic hormone (ACTH) response and decreased cortisol response after CRF administration[51]

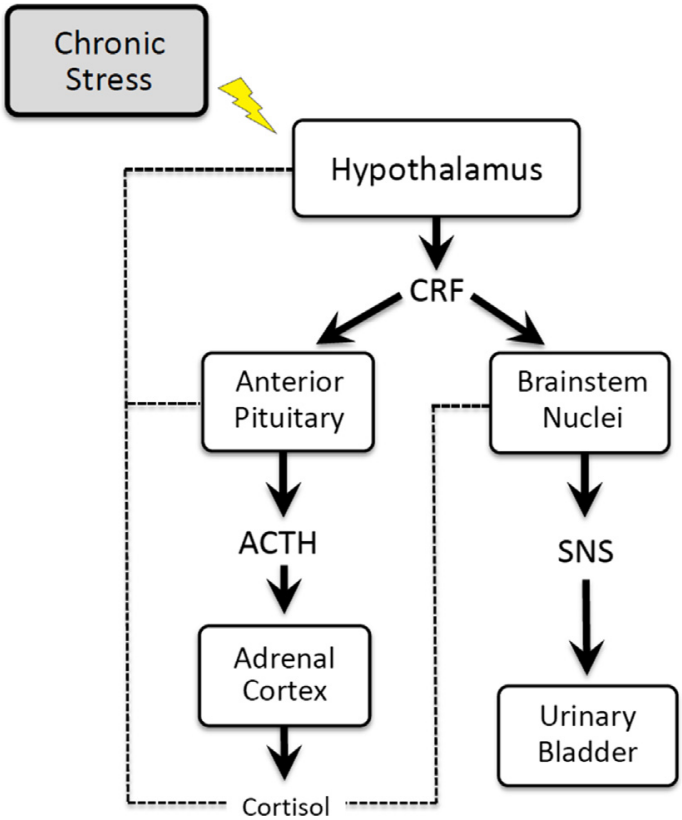

Fig. 2. Relationship between stress, the hypothalamic-pituitary-adrenal axis, and sympathetic nervous system (SNS) in cats with FIC. Perceived stress results in release of CRF from the hypothalamus. This causes the anterior pituitary to release ACTH and the brainstem nuclei activate the SNS, resulting in production of catecholamines (epinephrine and norepinephrine). In normal cats, corticosteroids have a negative feedback effect on the hypothalamus, anterior pituitary, and brainstem (*dotted line*). In cats with FIC, the excitatory SNS is inadequately restrained by cortisol and other adrenocortical steroids. The enhanced sympathetic activity is thought to increase tissue permeability in the urinary bladder, resulting in increased sensory afferent activity and the typical clinical signs of FIC. Feedback inhibition at the level of the anterior pituitary and hypothalamus also is reduced in cats with FIC, which tends to perpetuate CRF output. Solid line indicates stimulation; dotted line indicates inhibition. (*Adapted from* Westropp JL, Tony Buffington CA. FIC: current understanding of pathophysiology and management. Vet Clin North Am Small Anim Pract 2004;34(4):1043–55; with permission.)

- Smaller adrenal glands[52]
- Higher plasma catecholamine concentrations and increased urinary bladder permeability[53]

Given that systemic effects of stress are not limited to the urinary bladder, why do LUT signs predominate in cats with FIC? The anatomic proximity of the micturition and fear pathways, which overlap via connections from the amygdala to the periaqueductal gray, may be a factor. The periaqueductal gray is an anatomic and functional interface between the forebrain and lower brainstem; it has a major role in integrated behavioral responses to internal (eg, pain) or external (eg, threat) stressors. This connection may place the bladder at increased risk for activation during stress responses.[54] Documentation of involvement of other organ systems in cats with FIC also supports a role for neuroendocrine involvement. Indeed, cats often present with various comorbidities related to gastrointestinal, respiratory, dermatologic, and behavioral signs (nervousness/fearfulness).[4–6,47] Although much remains unknown, it is clear that the pathophysiology of FIC likely involves complex interactions between various body systems and is not just a "bladder disease."

DIAGNOSTIC APPROACH

On initial presentation, owners usually report acute onset of various combinations of signs related to LUT disease and/or urinary obstruction (periuria, pollakiuria, stranguria, dysuria, discolored urine due to hematuria). Physical examination of nonobstructed cats may include a small or minimally distended urinary bladder with thickened walls. Because these findings are nonspecific and FIC is a diagnosis of exclusion, other causes of LUT dysfunction must be eliminated (**Table 3**). At a

Table 3
Diagnostic evaluation of cats with nonobstructive lower urinary tract signs

Clinical Presentation	Relative Prevalence (%)	Most Common Primary Disease(s) to Exclude	Recommended Diagnostic Tests
Acute self-limiting episodes	80–90	Uroliths	Urinalysis Survey radiographs
Frequently recurring episodes	2–15	Uroliths Behavioral disorders Urinary tract infection	Urinalysis Survey radiographs Behavioral history[a] Quantitative urine culture
Chronic, persistent episodes	2–15	Uroliths Behavioral disorders Urinary tract infection Neoplasia Anatomic defects[b]	Urinalysis Survey radiographs Behavioral history[a] Quantitative urine culture Ultrasonographic examination Contrast cystourethrography

[a] For periuria, behavioral history should include information on the duration and location of inappropriate urination and material/substrate preferred by the cat (type of litter, rate of litter box cleaning, location and number of litter boxes). Household information should include number of cats and other pets and how they share the space, relationship with people, enrichment, and recent changes in environment.

[b] Anatomic defects reported in cats include urethral strictures, ectopic uterine horn entering the urinary bladder, patent urachus, urachal diverticula, ectopic urethra, and urethrorectal fistula.

Adapted from Lulich J, Osborne C, Kruger J. What constitutes a diagnosis of feline idiopathic cystitis? Proc ACVIM Forum 2010;630–1.

minimum, a urinalysis with sediment evaluation and survey abdominal radiographs should be performed on cats presenting with LUT signs. Because cats with FIC often have clinical signs outside the LUT that may be overlooked by both owners and clinicians, a complete history and physical examination of all organ systems as well as a detailed environmental history should be collected in all cats with LUT signs.[55]

EVIDENCE-BASED MANAGEMENT

In most cats with nonobstructive FIC, clinical signs resolve within 1 to 7 days without therapy.[23,56,57] However, up to 65% of cats with acute FIC will experience one or more recurrences of clinical signs within 1 to 2 years.[23,56,57] In a small percentage of cats (~15%), clinical signs persist for weeks to months or are frequently recurrent; these cats are classified as having chronic FIC. The generally self-limiting nature of clinical signs in most cats may explain why in the past decade greater than 80 agents or procedures have been recommended for cats with FIC.

Because most signs resolve in about a week, with or without therapy, almost any treatment may seem beneficial, emphasizing the critical need for applying principles of evidence-based medicine when selecting the best treatment options for cats with FIC. Veterinarians making therapeutic decisions should consider the quality of evidence supporting a recommendation to use (or not use) a particular treatment. Whenever possible, recommendations should be based on results of randomized and controlled scientific studies (ie, the highest quality of evidence), because this is the best predictor of results likely to occur in clinical patients.[58] In the absence of such studies, one should recognize inherent limitations of recommendations based on less secure forms of evidence. For dealing with such limitations, one suggested method is to assign a score defining the strength and quality of evidence, where grade I is the highest and grade IV is the lowest (**Box 1**).[58,59] The later discussion focuses on the evidence supporting commonly recommended treatments for cats with nonobstructive FIC. Although there are many recommended options, only a few have been carefully studied in cats with naturally occurring FIC.

Box 1
Description of grades use to classify evidence

Grade	Description of Evidence
I	At least one properly designed, randomized, controlled clinical study conducted in patients of the target species with naturally occurring disease living in pet owner's home
II	Evidence from properly designed, randomized, controlled studies in animals of the target species with naturally occurring disease living in a laboratory or colony environment
III	Appropriately controlled studies without randomization; appropriately designed case-control epidemiologic studies; animal models of disease in the target species; dramatic results from uncontrolled studies; case series
IV	Studies conducted in nontarget species; reports of expert panels; descriptive studies; case reports; pathophysiologic rationale; expert opinion

Abbreviations: I, highest quality; IV, lowest quality.

Adapted from Roudebush P, Allen TA, Dodd CE, et al. Application of evidence-based medicine to veterinary clinical nutrition. J Am Vet Med Assoc 2004;224:1766–71; and Roudebush P, Allen TA, Novotny BJ. Evidence-based clinical nutrition. small animal clinical nutrition. 5th edition. Topeka (KS): Mark Morris Institute; 2010. p. 23–30.

STRESS MANAGEMENT

Environmental Enrichment

Over the last 40 years, sociologic stress research in humans confirms that when stressors are methodically measured, their impacts on physical and mental health are substantial.[60] Preoperative stress and anxiety have been shown to predict postoperative pain in human orthopedic patients.[61] Studies in IC patients support an association between life stress and increased severity and frequency of clinical signs[62]; this is consistent with reports of stress-related exacerbations in other conditions that involve neurogenic inflammatory mechanisms (eg, rheumatoid arthritis, IBD, psoriasis).[45,63,64] Interestingly, placebo-treated IC patients attributed their statistically significant reduction in clinical signs, in part, to feeling decreased stress while in the study.[65] The authors recommended providing IC patients with advice and support, including nutritional recommendations and stress reduction, before starting medical therapy.

Because of documented abnormalities in the neuroendocrine system, treatment aimed at decreasing central noradrenergic drive (eg, stress) is also important for managing cats with FIC. Environmental enrichment is one method of decreasing stress, particularly for indoor-housed cats. In this context, the goal of environmental enrichment is to increase behavioral choices and draw out species-appropriate behaviors.[66] For indoor-housed cats with FIC, strategies include enhancing interactions with owners, minimizing conflict, providing all necessary resources, and making any changes gradually.[49]

In general, predictable routines and interactions with owners may help reduce stress in the cat. Some simple interventions that can improve intercat relations include providing an abundance of resources; placing a cat-safe belled collar on aggressor cat or cats, and partial or full segregation of the cats. For severe cases, consultation with a veterinary behaviorist for a comprehensive behavioral modification program that includes desensitization and counterconditioning should be considered. An abundance of feline resources, including toys and play activities and sites for watering, feeding, scratching, elimination, and resting/perching, should be spread throughout the home. A standard rule is to provide as many resources as there are cats plus an additional one. Litter box care and maintenance are also part of an enriched environment. In general, cats prefer clumping litter with sandlike texture in large uncovered boxes placed in quiet, easily accessible locations; however, preferences in individual cats may be highly variable.[67] As with other resources, there should be at least one litter box per cat, and one more litter box than the number of cats in the household is ideal. More detailed information on environmental enrichment is available.[68,69]

Supporting evidence

Although environmental enrichment has been recommended for cats with FIC and is thought to be beneficial, it has not been evaluated in a randomized controlled clinical trial. The best evidence supporting environmental enrichment comes from a controlled laboratory study of cats with naturally occurring disease (grade II), an uncontrolled, prospective clinical study in cats with FIC (grade III), pathophysiologic rationale, clinical experiences, and expert opinion (grade IV). A controlled laboratory study measured a variety of parameters in FIC-affected cats when exposed to stressful versus enriched environments.[53] Catecholamine concentrations and urinary bladder permeability decreased during the enrichment phase, suggesting environmental enrichment may have a beneficial effect for cats with FIC.[53] A prospective observational study (grade III) reported the effects of multimodal environmental modification in 46 client-owned cats with FIC.[5] There were significant reductions in LUT signs, fearfulness, and nervousness after treatment for 10 months. Veterinary specialists and

behaviorists agree (grade IV) that housing cats indoors can be stressful when their environment lacks outlets for natural behaviors, such as scratching, chewing, elimination, resting/hiding, and hunting/playing.[70,71]

Recommendations

- Institute environmental enrichment and methods to reduce stress as part of the initial management of all cats with FIC.
- Consult additional resources for helpful information that can be used by veterinarians and cat owners.[68,70–75]

Feline Facial Pheromone

Pheromones are bioactive compounds emitted and detected by animals of the same species that influence social and reproductive behavior. Classically, pheromones are described as nonvolatile molecules that regulate innate social behavior by activating vomeronasal organ sensory neurons. Recent studies suggest this definition may be too restrictive. It appears that pheromones may activate vomeronasal or main olfactory epithelium neurons and may have their effects altered by context as opposed to being strictly innate.[76] Synthetic feline facial pheromone therapy has been recommended as a method to decrease signs of stress in cats with FIC.[77,78]

Supporting evidence

A recent systematic review of the scientific literature on the use of pheromones in cats with and without FIC concluded that, based on 7 published studies, there is insufficient evidence to support the use of feline facial pheromones to manage FIC, to decrease stress in hospitalized cats, or to calm cats in unfamiliar surroundings.[79] At this time, their use in cats with FIC is supported by grade IV evidence (pathophysiologic rationale).

Recommendations

- There is insufficient evidence to support the use of feline facial pheromones to manage FIC.
- It is possible feline facial pheromones may be helpful in some individual cats with FIC and could be used after recommending other treatments that are supported by higher grades of evidence.

Supplements/Therapeutic Foods for Stress

For centuries, practitioners of traditional Chinese medicine have recommended nutritional supplements as therapy for behavioral conditions such as anxiety or stress. Natural treatments, including amino acids, minerals, and fatty acids, have been shown to have beneficial effects on neurotransmitter concentrations and signs of anxiety in animal models and humans.[80] The neurotransmitter serotonin has remarkable modulatory effects in almost all central nervous system integrative functions, such as mood, anxiety, stress, aggression, feeding, cognition, and sexual behavior.[81] Increased concentrations of serotonin have been associated with decreased anxiety in people and animal models.[82] Cow's milk has long been considered to have natural "tranquilizing" properties. Milk protein hydrolysate is derived from milk (also known as hydrolyzed casein and α-casozepine) and has been associated with significant alleviation of stress in models of anxiety in rodents and people.[83] The exact mechanism of these anxiolytic effects is unknown but may be mediated through the γ-amino butyric acid/benzodiazepine receptor complex.[84]

Supporting evidence

Positive effects of various nutrients on anxiety and stress-related behaviors in mammals have been reported for L-tryptophan and milk protein hydrolysate. L-Tryptophan, a precursor for serotonin synthesis, has been evaluated as a method of managing stress-related behaviors in cats in one blinded placebo-controlled study (grade I).[85] In this 2-month study, the authors observed significant changes in a variety of behaviors, suggesting that L-tryptophan supplementation changed the frequency of stress-related behaviors, decreasing signs of anxiety. One multicenter grade I (placebo-controlled, blinded) study evaluated the anxiolytic effects of α-casozepine (Zylkene) in 34 cats (n = 17 placebo, n = 17 α-casozepine).[86] At the end of the study, 10 of the 14 cats judged to have a successful outcome were from the α-casozepine group. This study provides evidence for the efficacy of α-casozepine in the management of anxiety in cats, including socially stressful conditions. These studies provide grade I evidence for short-term relief of clinical signs; however, studies of greater duration would be helpful because of the waxing and waning nature of FIC episodes over time. Although evidence supports positive benefits of these compounds, daily administration of oral medications may be stressful for some cats. Providing a multipurpose therapeutic urinary food that contains specific nutrients with proven antianxiety benefits is a novel approach to stress management in cats with FIC.

Recommendations

- If oral administration does not increase stress, consider recommending L-tryptophan 12.5 mg/kg and or α-casozepine 15 mg/kg (Zylkene) in conjunction with implementing environmental enrichment in FIC cats with clinical signs of stress.
- Consider including a specific nutritional recommendation for a therapeutic urinary food containing nutrients with antianxiety benefits in conjunction with implementing environmental enrichment in FIC cats with clinical signs of stress.

NUTRITIONAL MANAGEMENT

Moist Food/Increased Water Intake

Increasing water intake by feeding moist food, increased sodium intake, and addition of broth or other methods may or may not be beneficial for cats with FIC. Of these methods, feeding moist food is the only method that has been evaluated in cats with FIC. Theoretically, diluting the urine via additional water intake could dilute potential noxious stimulants such as urea and potassium chloride. However, the exact role these noxious stimulants play in the pathogenesis of FIC remains unknown.

Supporting evidence

Two studies have documented some benefits associated with feeding moist foods to cats with FIC.[56,87] In a 1-year, nonrandomized prospective (grade III) study of 46 cats with FIC, feeding a moist therapeutic food (Waltham Veterinary Feline Control pHormula Diet in Gel) was associated with significant improvement compared with feeding a dry version of the food.[87] At the end of the 1-year study, recurrence of clinical signs in cats eating moist food was significantly less (11% of 18 cats) compared with cats eating dry food (39% of 28 cats) ($P = .04$). Compared with the dry food group, urine specific gravity was significantly less in cats eating moist food; throughout the 1-year study, mean urine specific gravity values ranged from 1.032 to 1.041 in cats eating moist food and from 1.051 to 1.052 in cats eating dry food ($P<.05$). In another study evaluating glucosamine in 40 cats with FIC, moist food was recommended for all cats in the treatment and control groups. Most owners (90%, or 36) increased amount of moist food given to their cats, and the majority (82.5%) began feeding moist food

exclusively. Most cats in both groups improved significantly compared with their condition at baseline, and mean urine specific gravity was significantly lower at the 1-month recheck compared with baseline (1.036 ± 1.010 vs 1.050 ± 1.007) ($P<.01$).[56] The change in urine specific gravity coincided with the change to moist food and initial improvement in mean monthly clinical scores. In both studies described above, increased consumption of moist food was associated with less concentrated urine (specific gravity (SG) <1.040), which may have resulted in improved clinical signs; however, it is also possible that other factors associated with feeding moist food (eg, texture, taste, owner-cat interactions associated with delivery of moist food) may have served as a form of environmental enrichment and had a positive impact on the cats' well-being.

Increased dietary salt intake has also been proposed as a method of diluting urine, including cats consuming dry foods; however, its effects have not been studied in cats with FIC.[88] In healthy cats, increased sodium intake may or may not result in decreased urine specific gravity and/or increased urine volume.[89–93] In a 2-week study (grade II) of healthy cats, increased salt intake (1.2% sodium, dry matter basis) resulted in significantly decreased urine specific gravity compared with feeding 0.46% sodium, dry matter basis; however, urine volume did not increase in the high-salt group.[91] The mean daily urine specific gravity of cats fed higher sodium was not less than 1.045 at any time. In a 2-year study of healthy cats, mean urine specific gravity (spot measurements) was significantly lower at 3 months in cats fed higher sodium, but was not different at 6, 12, or 24 months.[92] In a controlled, 6-month study (grade II) of 24 normal cats randomized to receive either a high-sodium food (290 mg/100 kcal sodium) or a control food (140 mg/100 kcal sodium), there were no differences in mean urine specific gravity between groups at baseline, 3, or 6 months and mean values were not less than 1.040 at any point.[93] If the benefit of feeding increased sodium to cats with FIC depends on consistent lowering of urine specific gravity over the long term, it may not be an effective strategy. In addition, although there are no apparent contraindications for feeding high-sodium foods to healthy cats, there are differing opinions regarding the safety of increased sodium intake in cats with undetected kidney disease.[90–94] Consumption of moist food exclusively, regardless of sodium content, may be the most effective method for long-term urine dilution in cats, and this needs further study.[95]

Recommendations

- If transition to a new food does not increase stress for the cat or owner, make a specific nutritional recommendation for moist food (ie, which product, amount to feed, how often to feed). See later discussion for evidence supporting a therapeutic urinary food in cats with FIC signs.
- To minimize stress, transition to the new food gradually (weeks to months) and allow cats to self-select by offering the new food in a separate container beside the current food.

Therapeutic Urinary Food

Currently, there is no cure for FIC; therefore, goals for treatment are to improve quality of life for cats and owners by reducing duration and severity of clinical signs, the rate of recurrence of clinical signs, and the risk for urethral obstruction. Although there is no known benefit of urine acidification or controlling magnesium and phosphorus intake in cats with nonobstructive FIC, it may be important for preventing urethral obstruction, a potentially life-threatening complication in male cats. Over the last 30 years, struvite has consistently been the primary mineral component of the majority of

urethral plugs submitted to the Minnesota Urolith Center.[96] In some cats with LUT signs, it can be challenging to definitively distinguish between FIC and struvite disease (urethral plugs or uroliths). Nutritional factors that may impact expression of LUT signs and help manage both FIC and struvite disease include the following:

- Decreasing urine concentrations of pro-inflammatory mediators and crystallogenic minerals
- Decreasing retention of crystals in the urinary tract
- Increasing urine concentrations of anti-inflammatory/proresolving mediators and crystallization inhibitors
- Increasing solubility of crystalloids in urine

Urinary bladder inflammation is characteristic of LUT disorders, including FIC and urolithiasis. Long-chain ω-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and antioxidants such as vitamin E, are potent anti-inflammatory agents.[97,98] Dietary fatty acids are absorbed and incorporated into cell membranes, including those of the urinary bladder, where they may alter production of inflammatory mediators. Effects of ω-3 fatty acids alone have not been evaluated in cats with LUT disorders; however, they seem to have beneficial urinary effects in studies of other species. In a study evaluating the chemopreventive efficacy of EPA and DHA in a rat model of bladder cancer, ω-3 fatty acids inhibited development of premalignant and malignant lesions.[99] This effect was attributed to the anti-inflammatory, antioxidant, antiproliferative, and antiangiogenic properties of ω-3 fatty acids. Oxidative stress and increased free radical-induced peroxidation of cell membrane phospholipids may cause tissue injury by impairing cell membrane functions and inducing production of inflammatory cytokines.[98] Vitamin E and β-carotene, both potent antioxidants, have been shown to protect against cyclophosphamide-induced oxidative damage to bladder tissue in rats.[16] Commercially available multipurpose therapeutic urinary foods vary considerably in their ω-3 and antioxidant content.[100] Although the optimal therapeutic dose of ω-3 fatty acids and antioxidants for cats with FIC have not been determined, a recent study supports the long-term use of a multipurpose therapeutic urinary food with enhanced concentrations of these nutrients in cats with FIC.[101,102]

Supporting evidence

A recent prospective, randomized, double-masked (grade I) study evaluated the efficacy and safety of a multipurpose therapeutic urinary food, enriched with ω-3 fatty acids (EPA and DHA) and antioxidants (vitamin E and β-carotene), for the long-term management of acute FIC.[101–103] For the duration of the 12-month study, owners chose to offer either wet or dry food exclusively and then cats were randomly assigned to the test or control food groups. The test food was a commercially available multipurpose therapeutic urinary food (Hill's Prescription Diet c/d Multicare Feline), and the control food was custom manufactured and formulated to meet or exceed Association of American Feed Control Officials nutrient requirements for maintenance of adult cats. The mineral concentrations of the control food were designed to be similar to common grocery brands. Compared with the test food, the control food contained substantially lower concentrations of antioxidants and ω-3 fatty acids (EPA and DHA) (**Table 4**).

The primary endpoint was the frequency of recurrent episodes of LUT signs within 12 months. Twenty-five cats ranging in age from 1 to 9 years were included; 11 cats (5 males, 6 females) were fed the test food and 14 cats (11 males, 3 females) were fed the control food. Data were analyzed as a binomial proportion of the number of days that

Table 4
Selected nutrient values for test food compared with control food evaluated in a 1-year, randomized, controlled clinical study of cats with feline idiopathic cystitis

Nutrient Amounts (per 100 Kcal)	Test Food (Dry)	Test Food (Moist)	Control Food (Dry)	Control Food (Moist)
Protein (g)	9	10.7	8.7	11
Calcium (mg)	176	217	346	310
Phosphorous (mg)	182	209	291	289
Magnesium (mg)	17	19.5	29.4	25.4
Sodium (mg)	83	83	81	124
Vitamin E (IU)	24	30	1	3
Omega-3 EPA (mg)	53	65	4.6	10.5
Omega-3 DHA (mg)	36	44	2.7	10.5

Test food = Hill's Prescription Diet c/d Multicare Feline; Control food = custom manufactured maintenance food.

an event occurred or the number of episodes of LUT signs out of the total number of days a cat was in the study for a factorial arrangement of 2 foods and 2 formulations. Cats consuming the test food had a significantly lower proportion of total days with 2 or more clinical signs and total episodes of LUT signs ($P<.05$) with 4 of 11 (36%) test food group cats and 9 of 14 (64%) control food group cats exhibiting 2 or more clinical signs on at least one occasion during the 12-month study. The rate of recurrent episodes of LUT signs was 5 of 3904 days (1.28/1000 cat-days) in the test food group and 47 of 4215 days (11.15/1000 cat-days) in the control food group. This represents an 89% overall lower rate of recurrent episodes of LUT signs in cats fed the test food consistently compared with the control food (Fig. 3); this is the first study to definitively show that foods of different nutritional profiles impact the expression of LUT signs in cats with acute FIC.

Recommendations

- Make a specific nutritional recommendation for a multipurpose therapeutic urinary food (Hill's Prescription Diet c/d Multicare) to reduce rate of recurrent episodes of LUT signs in cats with FIC.
- Consider recommending therapeutic foods for struvite management when struvite disease cannot be excluded in cats with suspected FIC, especially those prone to urethral obstruction.

PHARMACOLOGIC THERAPY

Glycosaminoglycans

Treatment with GAGs (eg, pentosan polysulfate [PPS], glucosamine, chondroitin sulfate) has been suggested for cats with FIC because defects in the GAG layer covering the urinary bladder epithelium may play a role in the pathogenesis of the disease. Intravesical application of these agents seems to be useful in women with IC, a condition similar to FIC; however, a recent review of the literature concluded that additional large-scale trials are needed to confirm the benefit of this therapy.[104] Early studies

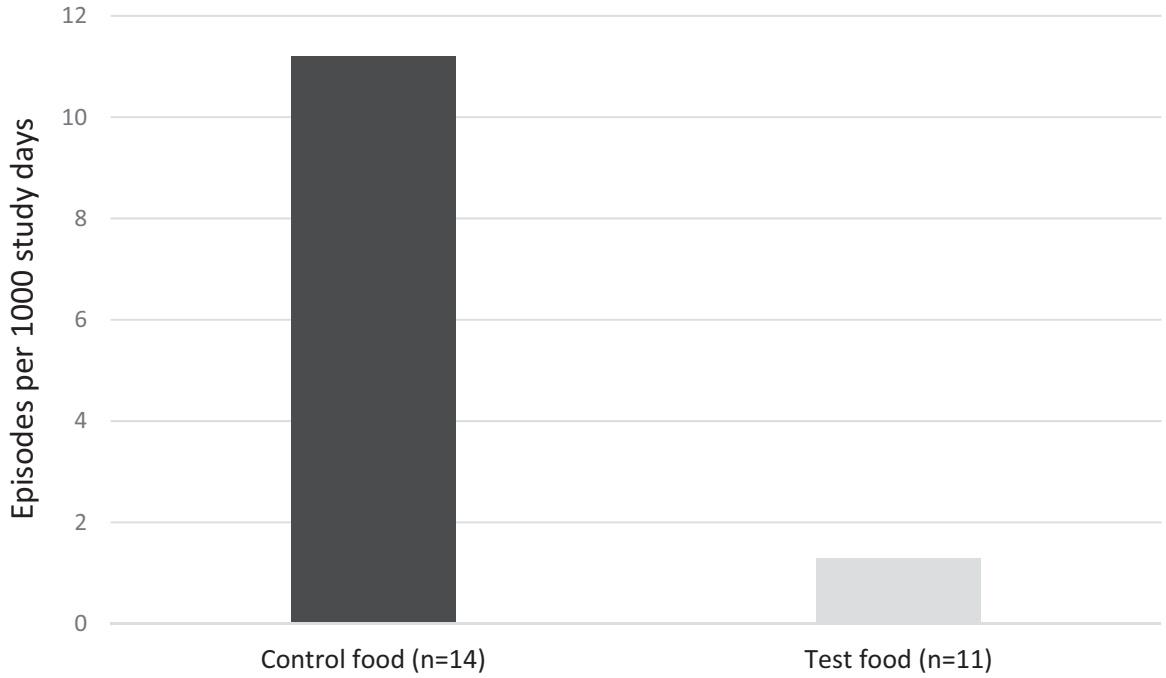

Fig. 3. Effect of feeding a test food for 1 year compared with control food on rate of recurrence of LUT signs in cats with FIC. Cats fed test food (Hill's Prescription Diet c/d Multicare) had a significantly lower proportion of total days with episodes of FIC signs ($P<.05$) compared with cats fed a control food.

suggested a positive effect of oral PPS in a proportion of human patients with IC.[105] However, a recent randomized, controlled clinical study in 368 adults with IC revealed no treatment effect versus placebo over 24 weeks at the currently established daily dose.[106] A similar trend has been reported in studies of cats with FIC.

Supporting evidence

A randomized, double-blind, placebo-controlled study was conducted to determine whether administration of glucosamine (Cystease, 125 mg administered per mouth once daily for 6 months; Ceva Animal Health) would reduce the severity or recurrence rate of clinical signs in cats with FIC compared with placebo.[56] Owner assessments suggested that glucosamine-treated cats achieved a slightly greater improvement by the end of the study (mean health score: 4.4 $\pm$ 0.7) compared with the placebo group (mean health score: 3.9 $\pm$ 1.6); however, this difference was not statistically significant ($P>.05$). There were no statistically significant differences in clinical signs between groups during treatment or at re-evaluation. A more recent randomized controlled study (grade I) confirmed that FIC cats receiving once daily oral administration of 250 mg *N*-acetyl-D-glucosamine (Cystaid) had increased the mean plasma GAG concentrations compared with placebo-treated cats ($P<.05$).[30] However, in the treated group, urine GAG-to-creatinine concentrations did not differ significantly from baseline or between the treated and placebo groups. Detailed information on severity and recurrence of clinical signs was not collected.

A randomized, double-blind, placebo-controlled study (grade I) was conducted to assess efficacy of subcutaneous injections of PPS (n = 9) versus placebo (n = 9) in cats with acute FIC.[107] During the year-long study, there was no statistically significant difference between cats treated with PPS and the placebo group, in either short-term or long-term follow-up. The authors concluded that PPS cannot be recommended for use in cats with FIC. However, only 6 cats (33%) had a recurrent episode and only one

cat had greater than one recurrence. A similar (grade I) study compared placebo with 3 oral doses of PPS in 107 cats with at least 2 episodes of LUT signs within the previous 6 months.[108] Clinical improvement occurred in all cats, regardless of the dose of PPS administration or changes in cystoscopic appearance of the bladder. These results indicate that PPS is equivalent to placebo for treatment of FIC.

Recommendations

- Currently, there is insufficient evidence to recommend oral or subcutaneous GAG therapy in cats with FIC.
- It is possible that GAGs could be helpful in individual cats; however, at this time its use is based on grade IV evidence (pathophysiologic rationale).

Amitriptyline

Amitriptyline (Elavil) is a tricyclic antidepressant with anticholinergic, antihistaminic, sympatholytic, analgesic, and anti-inflammatory properties that has been used in cats with FIC and in women with IC. A recent meta-analysis of randomized controlled trials in humans showed that amitriptyline had some beneficial effects in women with IC; however, the authors emphasized that only limited evidence exists for treatments recommended for painful bladder syndrome/IC, and more well-controlled studies are needed.[109]

Supporting evidence

In an uncontrolled (grade III) study of cats with severe recurrent FIC that failed to respond to other treatments, administration of amitriptyline for 12 months was associated with decreased clinical signs in 9 (60%) of 15 cats during the last 6 months of treatment.[110] A randomized controlled clinical trial (grade I) of amitriptyline treatment for 7 days revealed no significant difference in the rate of recovery from pollakiuria or hematuria; overall, clinical signs recurred significantly faster and more frequently in cats treated with amitriptyline compared with control cats.[57] In a similar grade I study, amitriptyline combined with amoxicillin was no more effective than placebo and amoxicillin when given for 7 days to cats with FIC.[111] Based on current information, amitriptyline does not seem to be beneficial for short-term management of cats with FIC. There is grade III evidence that longer use (minimum of weeks to months) may be helpful.

Recommendations

- There is insufficient evidence to recommend short-term treatment with amitriptyline.
- Consider long-term treatment with amitriptyline (5–10 mg per cat by mouth once daily) if cats with FIC continue to have recurrent episodes despite the use of treatments with a higher grade of evidence (ie, multipurpose therapeutic urinary food, feeding moist food, and environmental enrichment).

Anti-inflammatory Agents and Analgesics

In 2011, the American Urological Association provided guidelines for the diagnosis and treatment of IC/bladder pain syndrome in humans. Interestingly, the first-line treatments recommended for all patients include patient education, self-care practices, behavior modifications, stress management, and coping techniques.[112] However, because pain seems to be a prominent result of FIC, analgesics should be administered to help control these clinical signs. There have been no clinical trials

evaluating opioid analgesics (eg, butorphanol) or nonsteroidal anti-inflammatory drugs (NSAIDs), such as meloxicam, piroxicam, or robenacoxib, in cats with FIC.

Supporting evidence

Prednisolone (1 mg/kg administered by mouth twice daily for 10 days) was evaluated in a double-blind randomized controlled clinical trial of 12 cats with FIC and was found to be no more effective than placebo for reducing severity or duration of clinical signs in affected cats.[113] The best evidence supporting use of analgesics and NSAIDs comes from expert opinion and pathophysiologic rationale (grade IV).

Recommendations

- In addition to initiating stress reduction, environmental enrichment, and a specific nutritional recommendation, provide analgesia with narcotics such as buprenorphine (0.01 mg/kg orally every 8–12 hours), butorphanol (0.2 mg/kg subcutaneously or orally every 8–12 hours), or a fentanyl patch, depending on severity of pain/discomfort.
- NSAIDs should be used with caution in dehydrated patients because of the risk of reduced blood flow to the kidneys and potential for acute kidney injury. It is appropriate to contact the manufacturer for guidance when recommending a particular NSAID for individual patients.

SUMMARY

Two obstacles stand in the way of a cure for FIC: lack of an identifiable cause and a paucity of randomized controlled studies evaluating different treatment options. The same issues confound management of IC in human patients. As a result, current best evidence suggests a multimodal approach to patient management provides the best outcome for humans with IC.[114] Based on the current best evidence for cats with acute nonobstructive FIC, a multimodal approach is also advised; this includes a specific nutritional recommendation for a multipurpose therapeutic urinary food proven to reduce rate of recurrent episodes of FIC signs, environmental enrichment, and feeding moist food. Short-term analgesics are indicated to control signs of pain. The self-limiting nature of FIC and importance of environmental factors on recurrence of clinical signs emphasize the need for controlled, prospective, double-blinded clinical studies to determine the best management options for this complex condition.

REFERENCES

1. Osborne CA, Kruger JM, Lulich JP. Feline lower urinary tract disorders. Definition of terms and concepts. Vet Clin North Am Small Anim Pract 1996;26:169–79.
2. Buffington CA, Chew DJ, DiBartola SP. Interstitial cystitis in cats. Vet Clin North Am Small Anim Pract 1996;26:317–26.
3. Chew D, Buffington C. Pandora syndrome: it's more than just the bladder. In: Proc Am Assoc Fel Pract Conf. 2013.
4. Buffington CA. Idiopathic cystitis in domestic cats–beyond the lower urinary tract. J Vet Intern Med 2011;25:784–96.
5. Buffington CA, Westropp JL, Chew DJ, et al. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. J Feline Med Surg 2006;8:261–8.

6. Buffington CA, Westropp JL, Chew DJ, et al. Risk factors associated with clinical signs of lower urinary tract disease in indoor-housed cats. J Am Vet Med Assoc 2006;228:722–5.
7. Buffington CA. Comorbidity of interstitial cystitis with other unexplained clinical conditions. J Urol 2004;172:1242–8.
8. Buffington CA. External and internal influences on disease risk in cats. J Am Vet Med Assoc 2002;220:994–1002.
9. Freeman LM, Brown DJ, Smith FW, et al. Magnesium status and the effect of magnesium supplementation in feline hypertrophic cardiomyopathy. Can J Vet Res 1997;61:227–31.
10. Buffington CA, Chew DJ, Kendall MS, et al. Clinical evaluation of cats with non-obstructive urinary tract diseases. J Am Vet Med Assoc 1997;210:46–50.
11. Dorsch R, Remer C, Sauter-Louis C, et al. Feline lower urinary tract disease in a German cat population. A retrospective analysis of demographic data, causes and clinical signs. Tierarztl Prax Ausg K Kleintiere Heimtiere 2014;42:231–9.
12. Gerber B, Boretti FS, Kley S, et al. Evaluation of clinical signs and causes of lower urinary tract disease in European cats. J Small Anim Pract 2005;46:571–7.
13. Kruger JM, Osborne CA, Goyal SM, et al. Clinical evaluation of cats with lower urinary tract disease. J Am Vet Med Assoc 1991;199:211–6.
14. Lekcharosensuk C, Osborne CA, Lulich JP. Epidemiologic study of risk factors for lower urinary tract diseases in cats. J Am Vet Med Assoc 2001;218:1429–35.
15. Lund HS, Krontveit RI, Halvorsen I, et al. Evaluation of urinalyses from untreated adult cats with lower urinary tract disease and healthy control cats: predictive abilities and clinical relevance. J Feline Med Surg 2013;15:1086–97.
16. Saevik BK, Trangerud C, Ottesen N, et al. Causes of lower urinary tract disease in Norwegian cats. J Feline Med Surg 2011;13:410–7.
17. Pusoonthornthum R, Pusoonthornthum P, Osborne C. Risk factors for feline lower urinary tract diseases in Thailand. Thai Journal Veterinary Medicine 2012;42:517–22.
18. Lulich J, Osborne C, Kruger J. What constitutes a diagnosis of feline idiopathic cystitis? Proc ACVIM Forum 2010. 630–31.
19. Jones BR, Sanson RL, Morris RS. Elucidating the risk factors of feline lower urinary tract disease. N Z Vet J 1997;45:100–8.
20. Lund EM, Armstrong PJ, Kirk CA, et al. Prevalence and risk factors for obesity in adult cats from private veterinary US practices. Intern J Appl Res Vet Med 2005;3:88–96.
21. Egenvall A, Bonnett BN, Haggstrom J, et al. Morbidity of insured Swedish cats during 1999-2006 by age, breed, sex, and diagnosis. J Feline Med Surg 2010;12:948–59.
22. Cameron ME, Casey RA, Bradshaw JW, et al. A study of environmental and behavioural factors that may be associated with feline idiopathic cystitis. J Small Anim Pract 2004;45:144–7.
23. Defauw PA, Van de Maele I, Duchateau L, et al. Risk factors and clinical presentation of cats with feline idiopathic cystitis. J Feline Med Surg 2011;13:967–75.
24. Heidenberger E. Housing conditions and behavioural problems of indoor cats as assessed by their owners. Appl Anim Behav Sci 1997;52:345–64.
25. Lilly JD, Parsons CL. Bladder surface glycosaminoglycans is a human epithelial permeability barrier. Surg Gynecol Obstet 1990;171:493–6.
26. Parsons CL. Interstitial cystitis and lower urinary tract symptoms in males and females-the combined role of potassium and epithelial dysfunction. Rev Urol 2002;4(Suppl 1):S49–55.

27. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology 2007;69:9–16.
28. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991;145:732–5.
29. Buffington CA, Blaisdell JL, Binns SP Jr, et al. Decreased urine glycosaminoglycan excretion in cats with interstitial cystitis. J Urol 1996;155:1801–4.
30. Panchaphanpong J, Asawakarn T, Pusoonthornthum R. Effects of oral administration of N-acetyl-D-glucosamine on plasma and urine concentrations of glycosaminoglycans in cats with idiopathic cystitis. Am J Vet Res 2011;72:843–50.
31. Pereira DA, Aguiar JA, Hagiwara MK, et al. Changes in cat urinary glycosaminoglycans with age and in feline urologic syndrome. Biochim Biophys Acta 2004;1672:1–11.
32. Lavelle JP, Meyers SA, Ruiz WG, et al. Urothelial pathophysiological changes in feline interstitial cystitis: a human model. Am J Physiol Renal Physiol 2000;278:F540–53.
33. Birder LA, Wolf-Johnston A, Buffington CA, et al. Altered inducible nitric oxide synthase expression and nitric oxide production in the bladder of cats with feline interstitial cystitis. J Urol 2005;173:625–9.
34. Buffington CA, Teng B, Somogyi GT. Norepinephrine content and adrenoceptor function in the bladder of cats with feline interstitial cystitis. J Urol 2002;167:1876–80.
35. Hostutler RA, Chew DJ, DiBartola SP. Recent concepts in feline lower urinary tract disease. Vet Clin North Am Small Anim Pract 2005;35:147–70, vii.
36. Ikeda Y, Birder L, Buffington C, et al. Mucosal muscarinic receptors enhance bladder activity in cats with feline interstitial cystitis. J Urol 2009;181:1415–22.
37. Lemberger SI, Deeg CA, Hauck SM, et al. Comparison of urine protein profiles in cats without urinary tract disease and cats with idiopathic cystitis, bacterial urinary tract infection, or urolithiasis. Am J Vet Res 2011;72:1407–15.
38. Lemberger SI, Dorsch R, Hauck SM, et al. Decrease of Trefoil factor 2 in cats with feline idiopathic cystitis. BJU Int 2011;107:670–7.
39. Sant GR, Kempuraj D, Marchand JE, et al. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology 2007;69:34–40.
40. Treutlein G, Deeg CA, Hauck SM, et al. Follow-up protein profiles in urine samples during the course of obstructive feline idiopathic cystitis. Vet J 2013;198:625–30.
41. Treutlein G, Dorsch R, Euler KN, et al. Novel potential interacting partners of fibronectin in spontaneous animal model of interstitial cystitis. PLoS One 2012;7:e51391.
42. Wu CH, Buffington CA, Fraser MO, et al. Urodynamic evaluation of female cats with idiopathic cystitis. Am J Vet Res 2011;72:578–82.
43. Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: a retrospective 75 years after his landmark brief "letter" to the editor of nature. Stress 2012;15:472–8.
44. Qin HY, Cheng CW, Tang XD, et al. Impact of psychological stress on irritable bowel syndrome. World J Gastroenterol 2014;20:14126–31.
45. Martin TD, Chan SS, Hart AR. Environmental factors in the relapse and recurrence of inflammatory bowel disease: a review of the literature. Dig Dis Sci 2014. [Epub ahead of print].
46. Lutgendorf SK, Kreder KJ, Rothrock NE, et al. Stress and symptomatology in patients with interstitial cystitis: a laboratory stress model. J Urol 2000;164:1265–9.

47. Stella JL, Lord LK, Buffington CA. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. J Am Vet Med Assoc 2011;238:67–73.
48. Larauche M, Kiank C, Tache Y. Corticotropin releasing factor signaling in colon and ileum: regulation by stress and pathophysiological implications. J Physiol Pharmacol 2009;60(Suppl 7):33–46.
49. Westropp JL, Tony Buffington CA. Feline idiopathic cystitis: current understanding of pathophysiology and management. Vet Clin North Am Small Anim Pract 2004;34:1043–55.
50. Westropp JL, Buffington CA. Cerebrospinal fluid corticotrophin releasing factor and catecholamine concentrations in healthy cats and cats with interstitial cystitis. In: Proceedings Research Insights into Interstitial Cystitis. 2003.
51. Westropp JL, Buffington CA. Effect of a corticotropin releasing factor antagonist on hypothalamic-pituitary-adrenal activation in response to chronic renal failure in cats with interstitial cystitis. In: Proceedings Research Insights into Interstitial Cystitis. 2003.
52. Westropp JL, Welk KA, Buffington CA. Small adrenal glands in cats with feline interstitial cystitis. J Urol 2003;170:2494–7.
53. Westropp JL, Kass PH, Buffington CA. Evaluation of the effects of stress in cats with idiopathic cystitis. Am J Vet Res 2006;67:731–6.
54. Brodal P. The Central nervous system. 4th edition. Oxford University Press, USA; 2010.
55. Chew DJ, Buffington CA. Diagnostic approach to cats with lower urinary tract signs. Hill's Global Symposium on feline lower urinary tract health. Prague, Czech Republic, April 23-24, 2014. p. 23–30.
56. Gunn-Moore DA, Shenoy CM. Oral glucosamine and the management of feline idiopathic cystitis. J Feline Med Surg 2004;6:219–25.
57. Kruger JM, Conway TS, Kaneene JB, et al. Randomized controlled trial of the efficacy of short-term amitriptyline administration for treatment of acute, nonobstructive, idiopathic lower urinary tract disease in cats. J Am Vet Med Assoc 2003;222:749–58.
58. Roudebush P, Allen TA, Dodd CE, et al. Application of evidence-based medicine to veterinary clinical nutrition. J Am Vet Med Assoc 2004;224:1766–71.
59. Roudebush P, Allen TA, Novotny BJ. Evidence-based clinical nutrition. Small animal clinical nutrition. 5th edition. Topeka (KS): Mark Morris Institute; 2010. p. 23–30.
60. Thoits PA. Stress and health: major findings and policy implications. J Health Soc Behav 2010;51(Suppl):S41–53.
61. Robleda G, Sillero-Sillero A, Puig T, et al. Influence of preoperative emotional state on postoperative pain following orthopedic and trauma surgery. Rev Lat Am Enfermagem 2014;22:785–91.
62. Rothrock NE, Lutgendorf SK, Kreder KJ, et al. Stress and symptoms in patients with interstitial cystitis: a life stress model. Urology 2001;57:422–7.
63. Overman CL, Bossema ER, van Middendorp H, et al. The prospective association between psychological distress and disease activity in rheumatoid arthritis: a multilevel regression analysis. Ann Rheum Dis 2012;71:192–7.
64. Hunter HJ, Griffiths CE, Kleyn CE. Does psychosocial stress play a role in the exacerbation of psoriasis? Br J Dermatol 2013;169:965–74.
65. Bosch PC. Examination of the significant placebo effect in the treatment of interstitial cystitis/bladder pain syndrome. Urology 2014;84:321–6.
66. Laule GE. Positive reinforcement training and environmental enrichment: enhancing animal well-being. J Am Vet Med Assoc 2003;223:969–73.

67. Neilson JC. The latest scoop on litter. Vet Med 2009;140–4.
68. Feline house-soiling: useful information for cat owners. J Feline Med Surg 2014; 16:770–1.
69. Neilson JC. Feline house soiling: elimination and marking behaviors. Vet Clin North Am Small Anim Pract 2003;33:287–301.
70. Herron ME, Buffington CA. Environmental enrichment for indoor cats: implementing enrichment. Compend Contin Educ Vet 2012;34:E3.
71. Radosta L. Environmental enrichment for cats. Clinician's Brief 2014;13–5.
72. Buffington CA. Keeping cats indoors. Indoorpetosuedu. Columbus (OH): The Ohio State University Veterinary Medical Center; 2013.
73. Buffington CA. The indoor pet initiative. 2013. Available at: www.indoorpet.osu.edu. Accessed March 12, 2015.
74. Herron ME, Buffington CA. Environmental enrichment for indoor cats. Compend Contin Educ Vet 2010;32:E4.
75. ISFM A. Your cat's environmental needs. 2013. Available at: www.catvets.com. Accessed March 12, 2015.
76. Stowers L, Marton TF. What is a pheromone? Mammalian pheromones reconsidered. Neuron 2005;46:699–702.
77. Griffith CA, Steigerwald ES, Buffington CA. Effects of a synthetic facial pheromone on behavior of cats. J Am Vet Med Assoc 2000;217:1154–6.
78. Gunn-Moore DA, Cameron ME. A pilot study using synthetic feline facial pheromone for the management of feline idiopathic cystitis. J Feline Med Surg 2004;6: 133–8.
79. Frank D, Beauchamp G, Palestrini C. Systematic review of the use of pheromones for treatment of undesirable behavior in cats and dogs. J Am Vet Med Assoc 2010;236:1308–16.
80. Alramadhan E, Hanna MS, Hanna MS, et al. Dietary and botanical anxiolytics. Med Sci Monit 2012;18:Ra40–8.
81. Olivier B. Serotonin: a never-ending story. Eur J Pharmacol 2014. [Epub ahead of print].
82. Zhou J, Cao X, Mar AC, et al. Activation of postsynaptic 5-HT1A receptors improve stress adaptation. Psychopharmacology (Berl) 2014;231:2067–75.
83. Meisel H. Multifunctional peptides encrypted in milk proteins. Biofactors 2004; 21:55–61.
84. Miclo L, Perrin E, Driou A, et al. Characterization of alpha-casozepine, a tryptic peptide from bovine alpha(s1)-casein with benzodiazepine-like activity. FASEB J 2001;15:1780–2.
85. Pereira GG, Fragoso S, Pires E. Effect of dietary intake of L-tryptophan supplementation on multihoused cats presenting stress related behaviours. Birmingham (United Kingdom): BSAVA; 2010.
86. Beata C, Beaumont-Graff E, Coll V, et al. Effect of alpha-casozepine (Zylkene) on anxiety in cats. J Vet Behav 2007;2:40–6.
87. Markwell PJ, Buffington CA, Chew DJ, et al. Clinical evaluation of commercially available urinary acidification diets in the management of idiopathic cystitis in cats. J Am Vet Med Assoc 1999;214:361–5.
88. Markwell PJ, Buffington CT, Smith BH. The effect of diet on lower urinary tract diseases in cats. J Nutr 1998;128:2753S–7S.
89. Hawthorne AJ, Markwell PJ. Dietary sodium promotes increased water intake and urine volume in cats. J Nutr 2004;134:2128S–9S.
90. Kirk CA, Jewell DE, Lowry SR. Effects of sodium chloride on selected parameters in cats. Vet Ther 2006;7:333–46.

91. Luckschander N, Iben C, Hosgood G, et al. Dietary NaCl does not affect blood pressure in healthy cats. J Vet Intern Med 2004;18:463–7.
92. Reynolds BS, Chetboul V, Nguyen P, et al. Effects of dietary salt intake on renal function: a 2-year study in healthy aged cats. J Vet Intern Med 2013;27:507–15.
93. Xu H, Laflamme DP, Long GL. Effects of dietary sodium chloride on health parameters in mature cats. J Feline Med Surg 2009;11:435–41.
94. Buranakarl C, Mathur S, Brown SA. Effects of dietary sodium chloride intake on renal function and blood pressure in cats with normal and reduced renal function. Am J Vet Res 2004;65:620–7.
95. Burger IH, Smith PM. Effects of diet on the urine characteristics of the cat. Nutrition, Malnutrition and Dietetics in the Dog and Cat Proceedings of an International Symposium. London. 1987. p. 71–3.
96. Osborne CA, Lulich JP, Kruger JM, et al. Analysis of 451,891 canine uroliths, feline uroliths, and feline urethral plugs from 1981 to 2007: perspectives from the Minnesota Urolith Center. Vet Clin North Am Small Anim Pract 2009;39:183–97.
97. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006;83:1505S–19S.
98. Singh U, Devaraj S, Jialal I. Vitamin E, oxidative stress, and inflammation. Annu Rev Nutr 2005;25:151–74.
99. Parada B, Reis F, Cerejo R, et al. Omega-3 fatty acids inhibit tumor growth in a rat model of bladder cancer. Biomed Res Int 2013;2013:368178.
100. Forrester SD, Kruger JM, Allen TW. Feline lower urinary tract diseases. Small Animal Clinical Nutrition 2010;5:925–76.
101. Kruger JM, Lulich J, Merrills J, et al. A year-long prospective, randomized, double-masked study of nutrition on feline idiopathic cystitis. In: Proceedings American College of Veterinary Internal Medicine Annual Forum. 2013.
102. Lulich J, Kruger J, MacLeay J, et al. A randomized, controlled clinical trial evaluating the effect of a therapeutic urinary food for feline idiopathic cystitis. Hill's Global Symposium on Feline Lower Urinary Tract Health. Prague, Czech Republic. April 23-24, 2014. p. 55–9.
103. Kruger J, Lulich J, MacLeay J, et al. A randomized, double-masked, multicenter, clinical trial of two foods for long-term management of acute nonobstructive feline idiopathic cystitis (FIC). J Am Vet Med Assoc, in press.
104. Madersbacher H, van Ophoven A, van Kerrebroeck PE. GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans–a review. Neurourol Urodyn 2013;32:9–18.
105. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. Drugs 2006;66:821–35.
106. Nickel JC, Herschorn S, Whitmore KE, et al. Pentosan polysulfate sodium for treatment of interstitial cystitis-bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. J Urol 2014;193(3):857–62.
107. Wallius BM, Tidholm AE. Use of pentosan polysulphate in cats with idiopathic, non-obstructive lower urinary tract disease: a double-blind, randomised, placebo-controlled trial. J Feline Med Surg 2009;11:409–12.
108. Buffington T, Chew D, Kruger J, et al. Evaluation of pentosan polysulfate sodium in the treatment of feline interstitial cystitis—a randomized, placebo-controlled clinical trial. J Urol 2011;185:e382.
109. Giannantoni A, Bini V, Dmochowski R, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol 2012;61:29–53.
110. Chew DJ, Buffington CA, Kendall MS, et al. Amitriptyline treatment for severe recurrent idiopathic cystitis in cats. J Am Vet Med Assoc 1998;213:1282–6.

111. Kraijer M, Fink-Gremmels J, Nickel RF. The short-term clinical efficacy of amitriptyline in the management of idiopathic feline lower urinary tract disease: a controlled clinical study. J Feline Med Surg 2003;5:191–6.
112. Bosch PC, Bosch DC. Treating interstitial cystitis/bladder pain syndrome as a chronic disease. Rev Urol 2014;16:83–7.
113. Osborne CA, Kruger JM, Lulich JP, et al. Prednisolone therapy of idiopathic feline lower urinary tract disease: a double-blind clinical study. Vet Clin North Am Small Anim Pract 1996;26:563–9.
114. Rourke W, Khan SA, Ahmed K, et al. Painful bladder syndrome/interstitial cystitis: aetiology, evaluation and management. Arch Ital Urol Androl 2014;86:126–31.